REMARKS

Reconsideration is requested.

Claims 1-45 have been canceled, without prejudice.

Claims 46-69 have been added and are pending. No new matter has been added. Support for the claims may be found throughout the specification.

The specification has been amended as requested by the Examiner to include Sequence identifiers as well as the originally-published abstract. The specification has been amended to include the attached Sequence Listing. The attached paper and computer readable copies of the Sequence Listing are the same. No new matter has been added. A separate Statement to this effect is attached.

The heading for the figures has been amended to a more traditional form. A separate description of the additional parts of Figure 1 have also been added. No new matter has been added.

Withdrawal of the objections noted on page 2 of the Office Action dated November 5, 2002 (Paper No. 12) is requested. Similarly, withdrawal of the objection relating to the sequence rules compliance noted on page 3 of Paper No. 12 is requested.

The Section 101 rejection of claims 1-15 and 37-40 stated on page 3 of Paper No. 12 is moot in view of the above. The pending claims, which are directed to screening methods and proteins and nucleic acids which are isolated

are submitted to define patentable subject matter. The pending claims are not believed to encompass naturally occurring compounds. Moreover, process claims 46-51 recite active method steps of the claimed process. The claims are submitted to define patentable subject matter.

The Section 112, second paragraph, rejection of claims 1-27, 33-35, 37-42 and 44 stated on page 4 of Paper No. 12 is moot in view of the above. The pending claims are submitted to be definite and the Examiner is requested to consider the following in this regard.

The term 'H^+ gated' has been employed in the present claims rather than 'acid-sensitive'. 'H^+ gated' has a clear technical meaning to an ordinarily skilled person, who would immediately understand how low pH affects the protein. The ordinarily skilled person would have no difficulty in determining the metes and bounds of the claimed invention.

The term 'cation channel activity' also has a clear technical meaning. An ordinarily skilled person in the field understands this activity and how to measure the same and would have no difficulty in determining the metes and bounds of claims which employ this term.

Method claim 46 contains a preamble, method steps and a conclusion. It is clear what protein is exposed to the substance, what is being measured and how this is related to the activity of the substance. The ordinarily skilled person is familiar with a range of techniques for measuring ion channel activity in a cell

or membrane and would have significant experience of carrying out such techniques. The metes and bounds of the claim are therefore clear.

New claims 48 and 54 state the characteristics of the cation current which is mediated by the SPASIC protein. It is clear to an ordinarily skilled person what is meant by the 'rapid' and 'sustained' phases of the cation current.

Claims 57, 61 and 62 recite specific conditions which allow the hybridisation of nucleic acid sequences which are 80-90% identical.

The terms 'either', 'derivative', 'derived from' and 'allelic variant', which were found objectionable by the Examiner, are not included in the present claims, to advance prosecution and without prejudice.

The Section 101 rejection of claims 1-27, 33-35, 37-42 and 44 stated on pages 11-18 of Paper No. 12 is moot in view of the above. The pending claims are submitted to define patentable subject matter and consideration of the following in this regard is requested.

Following the revised USPTO Interim Utility Guidelines, the applicants submit that the analysis to be undertaken in considering 35 USC §101 is to determine whether a utility which is asserted in a specification is specific, substantial and credible. It is noted, firstly, that the Interim Utility Guidelines indicate that, as a general rule, treatments of specific diseases or conditions meet the criteria of 35 USC §101.

The specification asserts that the present invention has utility *inter alia* in the screening of analgesic and anti-inflammatory agents (see page 3 lines 3 to 6).

A 'specific' utility is specific to the subject matter claimed, rather than to the broad non-specific class which encompasses the invention. Whilst 'proteins' and 'nucleic acids' in general may have utility in 'screening methods', they do not have utility in the screening and identification of agents that are specifically analgesic and/or anti-inflammatory. Pain and inflammation are specific conditions and screening methods for agents to treat these conditions which employ the SPASIC ion channel have a specific utility.

A 'substantial' utility defines a 'real world' use and neither requires nor constitutes carrying out further research to confirm the 'real world' context. The asserted utility concerns the treatment of pain and/or inflammation, which are specified known medical conditions. Since pain and inflammation are common medical conditions, the provision of agents to treat these conditions is a desirable outcome based on a defined medical need and such agents possess a substantial and 'real world' utility. Screening methods to identify agents which themselves have a 'substantial utility' also have a 'real world' context of use. The subject matter of the invention therefore has a substantial utility.

A 'credible' utility is one believable to a person of ordinary skill based on the totality of evidence and reasoning provided. A utility is credible unless either

the logic underlying it is seriously flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the utility.

It is known in the art that acidosis accompanies many painful inflammatory and ischaemic conditions. The pain caused by this acidosis is furthermore known to be mediated by H+gated cation channels located in sensory neurons. The SPASIC channels described in the specification are H+gated cation channels which are expressed in sensory neurons. An ordinarily skilled person would understand that agents which block the SPASIC channel and thereby inhibit H+ gated cation channel activity in the membranes of sensory neurons, would reduce the pain caused by acidosis in various medical conditions. This rationale is consistent with the scientific facts and believable to an ordinarily skilled person. In the absence of serious flaws or inconsistencies in this logic, the utility would be credible to an ordinarily skilled person. It is further noted that the provision of new analgesic and anti-inflammatory agents using the present methods provides a significant benefit to the public.

The Examiner asserts that the functional properties of SPASIC cannot be predicted by comparison to other ion channels, given that no H+ gated channel having the properties of SPASIC has been characterised. However, in addition to sequence analysis, the H+ gated cation channel activity of the SPASIC channel has been demonstrated experimentally. Figure 2 of the specification shows that reducing pH stimulates an inward current in COS cells expressing

SPASIC. These experiments are further described in example 5. The activity of SPASIC is therefore not simply a matter of prediction, on the basis of similar ion channels, but is based on experimental evidence which confirms that SPASIC mediates the permeability of cations across a membrane in response to low pH and is therefore an H+ gated cation channel. Given the expression of SPASIC in sensory neurons, it is entirely credible to an ordinarily skilled person that SPASIC is responsible for all or part of the H+ gated cation channel activity which mediates acid responsive pain.

The Examiner asserts that the expression of SPASIC in sensory neurones does not mean that it is important in the management of pain and inflammation, since many proteins are found in sensory neurons, not all of which are important in the management of pain and inflammation. However, SPASIC protein described in the specification is not an anonymous, uncharacterised sensory neuron protein. The SPASIC protein is demonstrated to be both expressed in sensory neurons and to possess proton gated cation channel. Given the knowledge that proton gated cation channel activity in sensory neurons is known to be associated with pain and inflammation, the ordinarily skilled person would reasonably understand, absent evidence to the contrary, that SPASIC was involved in mediation of acid induced pain, and inhibitors of SPASIC would be useful in the treatment of such pain.

The function of SPASIC and disease states related to SPASIC function are clearly stated in the specification. The function of SPASIC is described on page 2 lines 9 to 27. Medical conditions which are associated with SPASIC activity are described on page 3 lines 3 to 8 and lines 22 to 28 and screening methods for agents useful in treating these conditions are described on page 24 line 25 to page 25 line 27.

The Examiner further asserts that the specification fails to disclose sufficient properties to support an inference of utility. Assignment to the family of ion channels is not considered to support an inference of utility because the members are not known to share a common utility. However, the Examiner notes that: '*some families of enzymes such as proteases, ligases, and telomerases share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family*'. See, pages 15-16 of Paper No. 12.

In fact, the application does not simply disclose 'a protein' or even 'an ion channel', but rather a sensory neuron ion channel which has proton gated cation channel activity. All members of the small subset of ion channels which are proton gated cation channels from sensory neurons show similar characteristics and share a common activity in directing the passage of cations such as Ca^{2+} and Na^{+} across the membrane of the neuron in response to low pH.

Given this common activity, all members of this subset of ion channels would be considered by an ordinarily skilled person to be involved in acid mediated pain transduction and therefore to share a common utility. Any proton gated cation channel that is expressed in sensory neurons would reasonably be expected to share this common utility. The identification of a member of the family of sensory neuron proton gated cation channels, based not only on structural similarity to known family members, but also on experimental verification (see figure 2 and example 5), is therefore sufficient to provide a specific, substantial and credible utility for the present invention.

For completeness, the applicants submit that the Examiner's reliance on Brenner v. Manson is misplaced, since the facts under consideration by the Supreme Court in Brenner v Manson were very different to those of the present case. In Brenner v Manson, the steroid produced by the process at issue had no disclosed activity or function. Although a homologue was known to have tumour inhibiting activity, the Court considered that there was insufficient likelihood that the steroid at issue had the same effect, given 'a greater known unpredictability of compounds in that field'. The present specification, by contrast, describes a polypeptide which is not only structurally related to known proton gated cation channels, but which is shown experimentally to possess proton gated cation channel activity. The role of this activity in the mediation of pain and its application for the screening of potential analgesics is also set out in the

specification. Given that there is no reason for an ordinarily skilled person to question this reasoning, the utility of the claimed invention is specific, substantial and credible in accordance with the principles set out in the USPTO Interim Utility Guidelines.

In summary, the specification provides screening methods which employ an ion channel which is shown experimentally to be a proton gated cation channel in sensory neurons. The channel shares a common mode of action with other known proton gated cation channels, in mediating an influx of cations across the cell membrane in response to reduced pH, and an ordinarily skilled person would reasonably impute that the agents which inhibit the SPASIC channel would be useful in the treatment of pain and the development of analgesics.

As for the corresponding Section 112, first paragraph rejection, the applicants submit that, for the reasons explained above, the claimed invention is supported by a specific, substantial and credible utility and one of skill in the art would be able to make and use the claimed invention, following the directions set out in the specification, without undue experimentation.

In determining whether experimentation is undue, *In re Wands* (noted by the Examiner) sets out various factors which must be considered. For the reasons set out below, consideration of these factors shows any experimentation required by the ordinarily skilled person in working the invention is not undue and

the disclosure of the specification therefore meets the requirements of 35 USC §112 first paragraph.

a) The nature of invention/scope of claims

The claimed invention relates to screening methods which employ SPASIC polypeptides as described in the specification. The genus of polypeptides covered by the present claims and defined using both structural and functional features to encompass polypeptides which are closely related to SEQ ID NO: 2. The sequence of SEQ ID NO: 2 thus defines the structure of all the members of the genus. The genus is further defined by the function of the polypeptide in mediating the proton gated cation permeability of a membrane.

An ordinarily skilled person would have a reasonable expectation that a polypeptide having a close structural relationship with SEQ ID NO:2, as set out in the claims, would possess the stated activity and would therefore be useful in screening methods of the invention.

b) Predictability of the art

The Examiner asserts that the effect of mutation on the structure and function of proteins is unpredictable.

However, polypeptides for use in the present screening methods are closely related an ordinarily skilled person would have a reasonable expectation that any variant protein which falls within the structural limitations set out in the claims is likely to possess the stated activity. This expectation may be tested in a

routine manner using the techniques described in the specification. Furthermore, key residues may also be identified by comparison with other proton gated channels, such as ASIC (see figure 1A –1D).

In the light of this teaching, it is clear to an ordinarily skilled person that the activity of polypeptides which fall within the claimed genus is, to a large extent, predictable and that most, if not all such polypeptides are likely to be useful in screening methods of the claimed invention.

c) Quantity of experimentation necessary

The Examiner suggests that a large quantity of experimentation is necessary to identify polypeptides with suitable structural and functional features for use in screening methods of the invention. This is not the case. Members of the genus of polypeptides useful in screening methods of the invention are structurally related to the polypeptide of SEQ ID NO:2. The identification and/or generation of polypeptides within this genus is routine for a skilled person in this field and requires the application of standard techniques with which the ordinarily skilled person is very familiar. Polypeptides which are closely related to SEQ ID NO: 2 are described in detail on page 4 line 35 to page 9 line 10 of the specification. An ordinarily skilled person is also very familiar with the techniques required for determining ion channel activity (see page 4 lines 21-28 and examples 5 & 6 of the specification).

The identification and characterisation of polypeptides suitable for use in screening methods therefore requires the routine use of conventional techniques. Given the defined breadth of the genus, the amount of routine experimentation required is low. Furthermore, it is noted that '*a considerable amount of experimentation is permissible, if it is merely routine.*'(In re Wands). Notwithstanding the above, the ordinarily skilled person is not required to undertake an extensive synthesis and screening program covering every conceivable polynucleotide that might be encompassed by the claims. Given the defined genus of nucleic acids which, for example hybridise to the complement of SEQ ID NO: 1 under the stated highly stringent conditions, there is a reasonable expectation that most if not all hybridising nucleic acids will have the stated activity. The ordinarily skilled person will need to test very few hybridising polynucleotides in order to identify a polynucleotide with the stated activity. The level of experimentation required to test these few polynucleotides using routine techniques is not undue.

d) Relative skill of those in the art

A person ordinarily skilled in the field of plant molecular biology at the filing date would have a high level of skill and experience in both the cloning and expression of ion channel genes and the determination of ion channel activity. The ordinarily skilled person would therefore be familiar with and experienced in

all the techniques required to carry out screening methods of the invention.

e) Amount of guidance provided by the inventors

Contrary to the Examiners assertion, there is significant guidance in the specification for the ordinarily skilled person to work the invention.

Variants and homologues of the sequence of SEQ ID NO: 2 are discussed in detail from page 4 line 35 to page 9 line 10 and in examples 3 and 4 of the specification. These passages teach how to identify variant sequences, both in terms of % homology, for example using sequence analysis software, and in terms of hybridisation to SEQ ID NO: 1 under stringent hybridisation conditions. Furthermore, the ordinarily skilled person is also taught how to test for SPASIC activity on page 4 lines 21-28, page 25 lines 9 to 27 and examples 5 & 6 of the specification.

The directions provided by the inventors in the specification provide ample guidance to allow the ordinarily skilled person to work the invention as claimed.

f) Existence of worked examples

The specification describes the screening of a cDNA library to identify a full-length SPASIC clone. This clone is tested for proton gated ASIC channel activity in example 5 and the screening of potential modulating agents is set out in example 6.

The inventors have therefore provided examples that show the working of the invention. An ordinarily skilled person would have no difficulty in following these examples to carry out the present invention.

In summary, an analysis of the factors set out in *In re Wands* indicates that the ordinarily skilled person could make and use the invention as claimed without undue experimentation and the present claims are therefore fully enabled by the present specification. The claims are supported by an enabling disclosure.

The Section 112, first paragraph, rejection of claims 2-14, "1627", 33-35, 37-42 and 44 stated on pages 22-27 it is moot in view of the above. The claimed invention is submitted to be supported by an adequate written description. Consideration of the following in this regard is requested.

New claim 46 is drawn to screening methods which employs a member of the genus of polypeptides at least 90% identical to SEQ ID NO: 2 which are proton gated cation channels. New claim 52 is drawn to the polypeptides themselves and new claim 55 is drawn to the genus of nucleic acids which encode such polypeptides.

There is a single species of each genus described with a complete structure, i.e. a screening method employing the polypeptide of SEQ ID No:2 (see example 6), the full length amino acid sequence of SEQ ID NO:2 and the nucleotide sequence of SEQ ID NO: 1 and its complement.

The procedures for producing polypeptide or nucleic acid molecules are conventional, e.g., any specified molecule can be produced recombinantly or ordered from a commercial synthesizing service. The procedures for screening for SPASIC activity are also conventional, and the specification describes assays for determining proton gated cation activity.

The specification discloses the sequences (SEQ ID NOs: 1 and 2) which define the structure of any polypeptide and nucleic acid molecules such that one ordinarily skilled in the art would be able to immediately envisage members of the genus embraced by claims 46, 52 and 55. The specification also discloses the functional characteristics of molecules within these genus, as well as a routine art-recognized method of screening for such molecules.

Only polypeptides which are structurally similar would possess the level of sequence identity set out in claims 46 and 52 and a person of ordinary skill in the art would not expect substantial variation among the polypeptide species which fall within the scope of the claim. The high level of sequence identity, in combination with the requirement for being an active SPASIC protein, along with the high level of skill and knowledge in the art, are adequate for the person of skill in the art to recognize that the specification discloses a representative number of species. The ordinarily skilled person would therefore recognize that the applicant was in possession of the genus of polypeptides and screening methods employing such polypeptides, as presently claimed.

Similarly, since only nucleic acid molecules which are structurally similar would hybridize under the high stringency conditions set out in claim 57, a person of ordinary skill in the art would not expect substantial variation among those nucleic acid species which fall within the scope of the claims. The highly stringent hybridization conditions, in combination with the requirement for encoding an active SPASIC protein and the high level of skill and knowledge in the art are adequate for the person of skill in the art to recognize that the specification discloses a representative number of species. The skilled person would therefore recognize that the applicant was in possession of the genus of nucleic acids of claim 57.

Given the above comments and the high general level of knowledge and skill in the art, one ordinarily skilled in the art would conclude that the applicant was in possession of the invention as presently claimed.

The Section 112, first paragraph, rejection of claim 26 noted on pages 27 and 28 of Paper No. 12 is moot in view of the above. The applicants note, for completeness, that CHO, COS and HEK 293 cells are standard cell types which are commonly used in biological research and are readily available from a range of commercial sources, including ATCC. An ordinarily skilled person would have no difficulty in using these cell types without reference to a particular deposit. Claims reciting these cell types are therefore fully enabled in the absence of a deposit.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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